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Latitude modifies the effect size of factors related to recurrent wheeze in the first year of life

Luis Garcia-Marcos [a,*], Javier Mallol [b], Dirceu Solé [c], Paul L.P. Brand [d,e], Maria Sanchez-Bahillo [f], Manuel Sanchez-Solis [a], the EISL Study Group [g]

[a] *Pediatric Respiratory and Allergy Unit, "Virgen de la Arrixaca" University Children's Hospital, University of Murcia, Ctra. Madrid-Cartagena, s/n. 30120 El Palmar, Murcia, Spain*
[b] *Department of Pediatric Respiratory Medicine, Hospital El Pino, University of Santiago de Chile (USACH), calle Camino los Morros 13560, San Bernardo, Santiago Metropolitan Region, Chile*
[c] *Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo (UNIFESP), Rua Pedro de Toledo 781, 9° andar, 04039-032 São Paulo, SP, Brazil*
[d] *Princess Amalia Children's Clinic, Isala Klinieken, Zwolle, The Netherlands*
[e] *UMCG Postgraduate School of Medicine, University Medical Centre Groningen, Postbus 10400, 8000 GK Zwolle, The Netherlands*
[f] *Department of Pediatrics, University of Murcia, Ctra. Madrid-Cartagena, s/n. 30120 El Palmar, Murcia, Spain*

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Summary
Background: Although the association between latitude and asthma prevalence has been studied to a certain extent, its influence on the magnitude of the association of risk/protective factors with recurrent wheeze in infants has never been reported.
Methods: The adjusted odd ratios (aOR) of various risk/protective factors for recurrent wheeze from 31 920 infants from 19 centres of the "Estudio Internacional de Sibilacias en Lactantes" (EISL) in very different parts of the world were used to build a meta-regression using the strength of the aOR of each factor as dependent variable and centre latitude as explanatory variable. The meta-regression was further adjusted for continent.
Results: There was a positive significant correlation between latitude and the magnitude of the aOR between recurrent wheeze and having cold(s) during the first three months of life ($p = 0.004$); attending a nursery school ($p = 0.011$); and having additional siblings

* Corresponding author. Tel.: +34 868888129; fax: +34 868888127.
E-mail address: lgmarcos@um.es (L. Garcia-Marcos).
[g] EISL study group listed at the end of the paper in the Appendix section.

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($p = 0.003$). Furthermore, there was a negative correlation for having been breastfed for at least three months ($p = 0.044$). Heterogeneity (as measured by I^2) of the magnitude of aORs between centres was quite high except for breast feeding: 73.1% for colds; 66.9% for nursery school; 52.6% for additional siblings; and 18.1% for breast feeding. Latitude explained a considerable amount of that heterogeneity: 63.8% for colds; 52.8% for nursery school; 86.6% for additional siblings; and 100% for breast feeding, probably as a consequence of its low heterogeneity.

Conclusion: The magnitude in which some risk/protective factors are associated to recurrent wheeze during the first year of life varies significantly with latitude.

Introduction

The influence of climate on the prevalence of asthma in children and adolescents has been shown in several studies.[1–4] As a possible surrogate of this factor, latitude has also been related to the prevalence of this condition in various countries, with certain findings indicating that asthma might be more frequent in areas near to the equator,[5–8] although those results are not totally consistent.[9,10] High latitude (no matter whether it be north or south) is related to colder weather and to lower exposition to sun and subsequent reduction of vitamin D. Furthermore, cold weather favours viral infectious diseases, and thus might trigger more frequent asthma episodes, and/or more incident cases of asthma.[6,11,12] However, latitude "per se" being a risk factor for asthma is one thing, and how latitude might modify the magnitude of the effect of other risk or protective factors is a very different one.

Wheezing in the first years of life will not necessarily develop into asthma in school ages in every child, and factors related to early wheezing might not be identical to those of asthma. Several epidemiological studies which have reported on the epidemiology of wheezing during the early months show that there are factors such as perinatal tobacco smoke exposure, respiratory infections by common viruses, preterm birth, poor housing conditions, indoor air quality, outdoor air pollution, mould stains on household walls, and obesity, which are associated with a higher prevalence of recurrent wheeze and physician-diagnosed asthma in the first two years of life.[13–22] Other factors, mainly breast feeding, are protective.[23,24] Recently, the "Estudio Internacional de Sibilancias en Lactantes" (EISL) (International Study of Wheezing in Infants) surveyed a huge number of one-year-old infants and reported a list of risk and protective factors for recurrent wheeze, defined as three or more episodes of this condition during the first year of life.[25] The study was carried out in a common time frame in a total of 17 centres in Latin America and Europe, and showed considerable variability in the magnitude of the association of those factors (measured as adjusted odds ratios, aOR), between centres. For instance, the overall most important risk factor, which was having symptoms of a cold during the first three months of life, ranged from aOR = 6.04 (95% CI 4.76—7.66) in Valdivia (Chile) to aOR = 2.03 (95% CI 1.26—3.29) in Bilbao (Spain). Similarly, the magnitude of the association of the most consistent protective factor, breast feeding, ranged from aOR = 0.58 (95% CI 0.42—0.81) in Santiago (Chile) to the non-significant association with aOR = 1.05 (95%CI 0.74—1.50) in Barranquilla (Colombia). Other risk or protective factors also showed a wide range variation in the magnitude of the association.[25]

The relatively high number of centres in the EISL study and their geographical dispersion, together with their sharing the same methodology, means that it offers a unique opportunity to analyse how latitude might modify the size of the effect of the main risk and protective factors on recurrent wheezing during the first year of life. The present study addresses this issue using the results of the aforementioned report[25] and incorporating the results of two additional centres in El Salvador and Honduras, which completed the study more recently.

Methods

Subjects

Recruitment of infants, questionnaire validation and how it was completed by parents have been described previously in detail.[13,25–28] Briefly, parents or guardians were invited to complete the questionnaire when infants were taken to their health centres for a scheduled vaccine administration or a preventive health care visit around the age of one year of life of their children. Samples close to at least 1000 infants were required from participating centres.

Definitions

Wheezing was defined as a positive answer to the previously validated question[13]: "Has your child had wheezing or whistling in the chest during the first 12 months of his/her life". Recurrent wheezing was defined as three or more parent-reported episodes of wheezing during the first year of life. Other definitions of risk or protective factors have been previously described.[25]

Statistical analysis

Adjusted ORs reported previously in 17 EISL centres together with those found in a more recent survey in San Pedro Sula (Honduras) and La Libertad (EL Salvador) were

included in the analysis. A total of 19 centres had data on the following significant risk/protective factors: gender, family history of asthma, family history of rhinitis, infant eczema, tobacco exposure during pregnancy, suffering from a cold during the first three months of life, attending a nursery school during the first year of life, duration of breast feeding, number of siblings, number of people at home, mould stains on the household walls, and studies of the mother.

Using Comprehensive Meta-Analysis (CMA) v2.2 software[29] a random effects meta-analysis of the analysed risk/protective factors from all 19 centres was performed and the summary OR was calculated for each factor. Furthermore, I^2 and its 95% confidence intervals were calculated in order to offer an estimation of heterogeneity, i.e. the proportion in which the observed variation between centres reflects real (as opposed to random) differences in the magnitude of the association. As a rule of thumb 25%, 50%, and 75% are cut-off points for low, medium, and high heterogeneity.[30]

A random-effect meta-regression, using the method of moments,[31] was used to calculate the correlation between the magnitude of the association (the value of aORs) for each factor and the degrees of latitude (irrespective of north or south), and its statistical significance. A graph of the regression line, with circle areas for centres proportional to weights (the inverse of the sum of the within trial variance and the residual between trial variance) given in the analysis, was also obtained.

In order to adjust for culturally-related factors the association between the Log(aOR) of each factor and latitude (per every 10°) was additionally adjusted for the continent (Europe vs. Latin America) in a multiple meta-regression, using the method of moments to estimate the additive (between-study) component of variance. The association was expressed as coefficients (slopes of the regression line) with their 95% confidence intervals and the corresponding *p* values. To express coefficients in a more explanatory way, they were additionally transformed into the percentage of increase or decrease of the size of the effect to which they were associated by transforming them into pseudo-OR as exp(coefficient).

An attempt was made to further adjust for hemisphere; however this was not possible as Europe is wholly in the Northern hemisphere, thus producing considerable colinearity between continent and hemisphere. Additionally, 19 centres hardly allow for a second adjusting variable. Moreover, when exploratory stratified (Northern vs. Southern hemisphere) analyses were performed, the results were rather similar to those obtained for the whole sample, irrespective of hemisphere.

Multiple regression analyses were performed using Stata v10 software package (College Station, TX, USA). As a way to further assess the significance of the correlation, a second *p* value using the Monte Carlo permutation ($n = 10{,}000$) test for meta-regression adjusted for multiple testing, was also obtained with this statistical package. For each factor, the *R*-squared of simple linear and multiple meta-regressions were calculated as an estimate of the percentage of heterogeneity (I^2) obtained in the random effects meta-analysis which is explained by latitude (unadjusted and adjusted for continent).

Results

The list of centres included and the analysis, their response rate, prevalence of recurrent wheezing and latitude are described Table 1.

The risk and protective factors included in the meta-regression together with the summary odds ratios resulting from the meta-analysis, which included values already published[25] together with those from two additional centres, i.e. La Libertad (El Salvador) and San Pedro Sula (Honduras), are shown in Table 2. The prevalence of the risk factors included in the present analyses is published elsewhere.[25]

In the bivariate analysis the strength of the association of three risk factors and one protective factor showed significant correlations with latitude. The magnitude of the association of having a cold during the first three months of life with recurrent wheezing in that period varied with latitude: the higher the latitude, the stronger the association (20.4% [95% CI 8.1%; 34.2%] increase per every 10°). Similarly, the higher the latitude, the stronger the risk of those attending a nursery school of having recurrent

Table 1 Centres, population, participation rate, prevalence of recurrent wheeze and latitude (data previously reported).[25,28]

	N	Response rate (%)	Recurrent wheezing (%)	Latitude (degrees)
Chile				
Santiago	2988	87	22.0	−33.4
Valdivia	3075	89	21.1	−39.5
Brazil				
Fortaleza	1209	90	22.1	−3.7
Recife	1063	89	25.0	−8.0
Belo Horizonte	2532	87	27.5	−19.9
Belem	3029	88	21.9	−1.4
Porto Alegre	1016	85	36.3	−30.0
Sao Paulo	1012	89	26.7	−23.6
Curitiba	3003	90	22.6	−25.4
Colombia				
Barranquilla	1688	85	15.9	11.0
Venezuela				
Caracas	3009	90	17.5	10.5
San Salvador				
La Libertad	1047	87	18.4	13.7
Honduras				
San Pedro Sula	780	84	11.7	15.5
Mexico				
Merida	1406	91	2.3	20.7
Spain				
Bilbao	996	70	18.6	43.3
Cartagena	1172	71	16.2	37.6
La Coruña	930	72	13.8	43.2
Valencia	886	61	12.1	39.5
The Netherlands				
Zwolle	1079	81	13.8	52.5

Table 2 Summary odds ratios (OR) from the random effects meta-analysis of the studied statistically significant risk/protective factors for recurrent wheezing during the first year of life, including the 16 centres previously reported[25] together with those in El Salvador and Honduras (adjusted for all factors in the table and also for having pets at home and ethnicity).

	Summary OR	95% CI	*p* value	I^2	95% CI
Male gender	1.56	1.40; 1.74	<0.0001	53.4	21.5; 72.3
Parental history of asthma	1.98	1.75; 2.25	<0.0001	50.0	15.1; 70.5
Parental history of rhinitis	1.46	1.29; 1.65	<0.0001	56.2	26.9; 73.8
Infant eczema	1.75	1.55; 1.96	<0.0001	53.2	21.2; 72.2
Mother smoked during pregnancy	1.50	1.30; 1.75	<0.0001	34.4	0.0; 62.3
Cold(s) during the first 3 months of life	3.00	2.59; 3.47	<0.0001	73.1	57.7; 82.9
Attended to a nursery school	2.49	2.06; 3.00	<0.0001	66.9	46.4; 79.5
Breast feeding for at least 3 months	0.80	0.73; 0.87	<0.0001	18.1	0.0; 52.7
Per additional sibling	1.06	1.01; 1.11	0.014	57.4	29.0; 74.4
Per additional person at home	1.04	1.02; 1.07	<0.0001	36.0	0.0; 63.1
Mould stains on the household walls	1.42	1.27; 1.60	<0.0001	45.8	7.2; 84.0
University studies in mother	0.81	0.71; 0.92	0.001	48.7	11.4; 70.3

wheeze in the first year of life (28.1% [95% CI 8.1%; 52.0%] increases per 10°); and the stronger the risk when exposed to an additional sibling (5.7% [95% CI 2.5%; 9.2%] increases per 10° latitude). With respect to the only protective factor (breastfeeding three or more months), protection was also higher when latitude was higher (8.8% [95% CI 1.8%; 15.3%] decrease per 10° increase in latitude) (Table 3 and Fig. 1). Other risk factors did not show any significant change in the magnitude of the association with changing latitude (Table 3). After adjusting for continent, the aforementioned correlations were maintained (Table 3). Fig. 2 depicts a graphical representation of the between centre variability explained by latitude.

Discussion

The results of the present study show that the magnitude of the associations of some risk or protective factors with recurrent wheezing during the first year of life differs with changing latitude. These associations (either positive or negative) are stronger as latitude increases. Having a cold during the first three months of life, attending a nursery school and having more siblings seem to increase their effect size in higher latitudes. This finding might be related to the fact that in colder climates viral respiratory infections —which cause the majority of wheezing episodes in infants[32] — might be more frequent and/or severe than when weather is milder.[33] However, it is quite possible that those findings cannot be generalised to other populations.

On the other hand, the mode of viral transmission might also play a role: in vivo studies have revealed that there is a direct effect of winter-like humidity on air-borne influenza transmission that dominates in regions with temperate climate, while influenza in the tropics is more effectively transmitted through direct contact. The effect of weather on transmission is quite variable and depends on what factors are introduced in models: for instance, Soebiyanto et al.[34] found that the best model for Hong-Kong influenza was obtained when land surface temperature, rainfall and relative humidity were included; conversely, for Maricopa County (Arizona) including either maximum atmospheric pressure or mean air temperature gave the best model.

Breast feeding tends to be more protective in higher latitudes, perhaps reflecting a higher "usefulness" of this protective factor in environments with either higher prevalence or severity of respiratory infections; or when the predominant way of transmission of viruses is different. This higher protection in higher latitudes might explain in part that recurrent wheezing episodes tend to be less frequent there.

The magnitude of the associations of the rest of the studied factors does not seem to be modified by latitude. Interestingly none of those factors is an environmental one; and thus, less likely to be modified by latitude. The magnitude of the association between gender, family or personal history of asthma and/or allergies and recurrent wheezing is not modified by latitude, despite the prevalence of those conditions being quite variable between centres included in the EISL.[28] The magnitude of the association of other factors not related to heritability, such as smoking habits of the mother during pregnancy, are also not modified by latitude, probably reflecting that an insult affecting the normal maturation of lungs is independent of external circumstances such as climate.

Having a higher education seems to be equally protective no matter what the latitude is, which may be consistent with the fact that mothers of higher education level probably live in a more hygienic environment. Therefore, they can better prevent respiratory infections to their children; are better prepared to deal with diseases in them; and can afford quicker and better medical attention. This comment should be contemplated under the perspective that this finding is controlled for nursery school attendance, which may be more frequent among mothers with a higher education.

Contrary to what might have been expected, the number of persons at home, which was a consistent risk factor for recurrent wheeze and might be related to more respiratory infections, did not change its strength with the changing latitude. This might be due in part to the relatively low heterogeneity of this factor (36%). Moreover, the magnitude of the risk of having mould stains on the household walls was neither modified by latitude, which may be related to the fact that indoor environment — humidity in the present case — may be quite independent of outdoor climate.

Table 3 Summary of unadjusted and adjusted (for continent) meta-regression coefficients (slopes) of the change of the association strength between the studied risk/protective factors and recurrent wheezing during the first year of life, according to 10° increase in latitude. Bold values signify statistically significant.

	Unadjusted					Adjusted[c]						
	Coeff.	95% CI	*p* value	*p* value[a]	R^2 (%)	Coeff.	95% CI	*p* value	*p* value[b]	R^2 (%)	% Change[d]	95% CI
Male gender	0.079	0.00005; 0.16	0.050	0.031	29.8	0.041	−0.064; 0.15	0.417	0.543	29.6	4.2	−6.2; 16.6
Parental history of asthma	−0.042	−0.142; 0.059	0.396	0.376	0.4	−0.074	−0.208; 0.059	0.258	0.338	3.4	−7.1	−18.8; 6.1
Parental history of rhinitis	−0.009	−0.106; 0.088	0.852	0.853	0	0.056	−0.072; 0.185	0.368	0.530	0	5.8	−6.9; 20.3
Infant eczema	0.075	−0.011; 0.161	0.082	0.050	24.8	0.052	−0.061; 0.167	0.343	0.417	18.3	5.3	−5.9; 18.2
Mother smoked during pregnancy	−0.020	−0.136; 0.095	0.712	0.719	0	−0.070	−0.226; 0.086	0.356	0.509	0	−6.7	−20.2; 34.2
Cold(s) during the first 3 months of life	**0.109**	**0.020; 0.198**	**0.020**	**0.015**	**46.6**	**0.186**	**0.078; 0.294**	**0.002**	**0.004**	**63.8**	20.4	**8.1; 34.2**
Attended to a nursery school	**0.182**	**0.063; 0.300**	**0.005**	**0.003**	**52.3**	**0.248**	**0.078; 0.419**	**0.007**	**0.011**	**52.6**	28.1	**8.1; 52.0**
Breast feeding for at least 3 months	**−0.063**	**−0.120; −0.006**	**0.033**	**0.061**	**100**	**−0.092**	**−0.167; −0.018**	**0.018**	**0.044**	**100**	−8.8	**−1.8; −15.3**
Per additional sibling	**0.054**	**0.029; 0.080**	**<0.0001**	**0.001**	**91.4**	**0.056**	**0.025; 0.088**	**0.001**	**0.003**	**86.6**	5.7	**2.5; 9.2**
Per additional person at home	−0.003	−0.024; 0.017	0.721	0.727	0	−0.0001	−0.025; 0.025	0.972	1.000	0	0.1	−2.4; 2.5
Mould stains on the household walls	0.058	−0.036; 0.152	0.209	0.196	16.5	0.035	−0.081; 0.152	0.531	0.688	9.2	3.5	−7.8; 16.4
University studies in mother	0.093	−0.015; 0.201	0.086	0.047	5.8	0.072	−0.061; 0.206	0.266	0.329	0	7.5	−5.9; 22.9

[a] According to Monte Carlo permutation ($n = 10{,}000$) test.
[b] According to Monte Carlo permutation ($n = 10{,}000$) test adjusted for multiple testing.
[c] Adjusted for continent (Europe vs. Latin America).
[d] Calculated from the adjusted model. A negative value means a decrease in the indicated percentage, while a positive value indicates an increase.

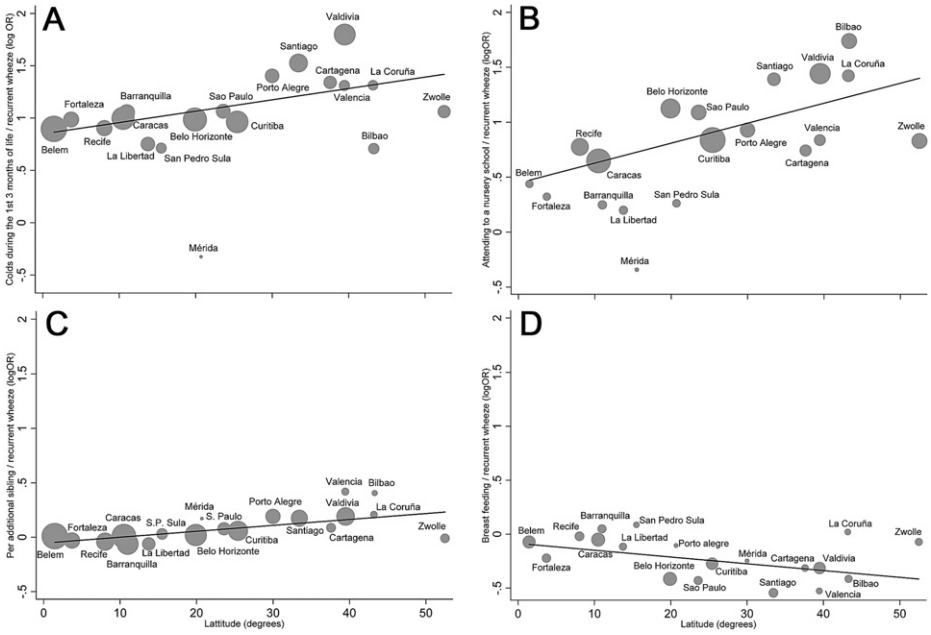

Figure 1 Meta-regression lines of the relation between degrees of latitude (regardless of north or south) and the strength of the associations [Log(aOR)] between recurrent wheeze during the first year of life and the following factors: A. Having at least one cold during the first three months of life; B. Attending to a nursery school any time during the first year of life; C. Per additional sibling at home; and D. Breast feeding at least three months. The size of the circles indicates the weight given to the different centres in the meta-regression analysis. It only includes those factors which showed their magnitude of association significantly correlated with latitude.

To the best of our knowledge no other study has analysed the influence of latitude on the strength of the associations between risk and protective factors for recurrent wheeze during the first year of life. Thus, the present results cannot be directly compared with other reports. Furthermore, we have not been able to retrieve any previous information regarding the influence of latitude itself, not on the strength of any association (which is the point of the present study), but even directly on the prevalence of asthma symptoms in infants or preschool children. However, several studies have reported some influence of latitude on the prevalence of asthma in schoolchildren and adolescents, with lower latitude being associated to a higher prevalence of asthma.[5–8,35] This finding is not consistent in

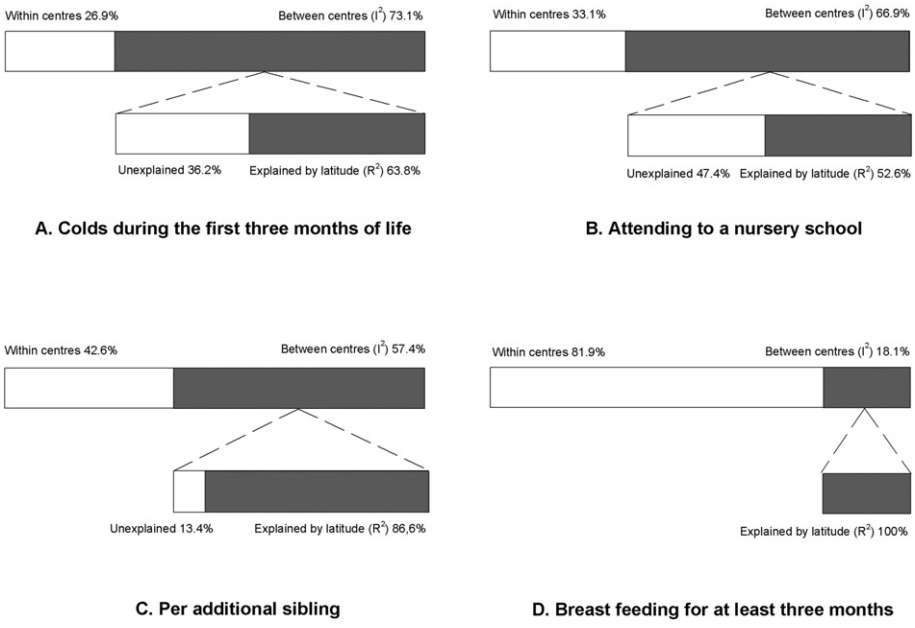

Figure 2 Graphical representation of the between centre variability explained by latitude. It only includes those factors which showed their magnitude of association significantly correlated with latitude.

all studies, as one of them did not find any association[10] and another one actually found an association with higher latitude.[9] In a recent and very large study including 56 centres in Latin America that were distributed in both hemispheres — from −53°S to 33°N — there was no significant correlation between the prevalence of current asthma symptom and latitude, altitude, or tropical setting.[36] Whether latitude has any influence on asthma prevalence through climate and its relation to viral infections[33,37] or to allergens[4] or through ultraviolet radiation and vitamin D[6,12,38] remains to be demonstrated. However, it should be kept in mind that wheezing in the first year of life does not necessarily develop into later asthma, thus studies on asthma at older ages should be interpreted with extreme caution when trying to extend their results to early wheezing.

Nevertheless, the present study was not designed to explore the association between latitude and the prevalence of asthma or recurrent wheeze, but to know how latitude may modify the magnitude of the association between several factors and the prevalence of recurrent wheeze. The main result of the present study is that while some factors might represent higher risk or protection in some areas, they may pose significant lower risk or protection in others; with latitude explaining some of those variations.

The present study has the main limitation of having a relatively low number of centres ($n = 19$). However, the fact that some significant results were found in the meta-regression with a somewhat low number of centres may be indicative of a true positive result: if the distribution of the magnitude of the ORs of the different factors throughout the centres were random, a significant result would have been very unlikely. Furthermore, the several significant results obtained point in the same direction, i.e. latitude might modify those factors associated to recurrent wheeze which are linked to respiratory infections in one way or another. Additionally, the present study is the only one to date which can offer data, obtained with a common methodology with a previously validated instrument and high response rate, on the epidemiology of infant wheezing from an acceptable number of centres with different latitudes throughout the world. On the other hand, the observational and ecological characteristics of the present study cannot be totally free of rest-confounding due to factors such as preterm birth, low birth weight, air pollution or gross national product.

In summary, latitude might significantly modify the strength of the association of risk and/or protective factors for wheeze during the first year of life.

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Ethical approval

The present study was approved by the Ethics Committee of the University of Murcia. Informed consent was obtained from parents before taking the questionnaire.

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Conflict of interest statement

None declared.

Appendix

EISL* Study Group:

Álvaro Madeiro Leite, Olivia Costa Bessa (Brazil, Fortaleza), Elaine Xavier Prestes (Brazil, Belem), Emanuel Sarinho, Décio Medeiros (Brazil, Recife); Paulo Camargos, Maria Jussara Fernández-Fontes, Wilson Rocha (Brazil, Bello Horizonte); Dirceu Solé, Caroline Della Bianca (Brazil, São Paulo); Nelson Rosario, Herberto Chong (Brazil, Curitiba); Gilberto B. Fischer (Brazil, Porto Alegre); Eduardo Cepeda (Colombia, Barranquilla); Oscar Aldrey, Arnaldo Capriles (Venezuela, Caracas); Javier Mallol, Viviana Aguirre, Alejandro Gallardo (Chile, Santiago); Mario Calvo (Chile, Valdivia); Manuel Baeza-Bacab, (México, Mérida); Margarita Figueroa (La Libertad, San Salvador); Agustín Bueso, Luis Cousin (San Pedro Sula, Honduras); Luis Garcia-Marcos, Antonela Martinez-Torres, Virginia Pérez-Fernández, Manuel Sánchez-Solís, Maria Sánchez-Bahillo (España, Murcia), Carlos González-Díaz, Andrés González Hermosa (España, Bilbao), Angel López-Silvarrey Varela (España, La Coruña), María Morales Suárez-Varela (España, Valencia); Paul L.P. Brand, Chantal AN Visser (Zwolle, The Netherlands).

*EISL for "Estudio Internacional de Sibilancias en Lactantes" (International Study of Wheezing in Infants).

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